

P^ATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 05 January 2001 (05.01.01)	
International application No. PCT/GB00/01759	Applicant's or agent's file reference REP06137WO
International filing date (day/month/year) 09 May 2000 (09.05.00)	Priority date (day/month/year) 10 May 1999 (10.05.99)
Applicant LOWE, Christopher, Robin et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 04 December 2000 (04.12.00)

☐ in a notice effecting later election filed with the International Bureau on:

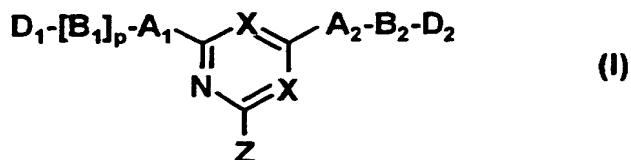
2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Juan Cruz Telephone No.: (41-22) 338.83.38
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CLAIMS

1. An affinity ligand-matrix conjugate comprising the matrix and, conjugated thereto by the group Z, a ligand having the general formula (I):



5 wherein one X is N and the other X is N, CCl or CCN;

A₁ and A₂ are each independently O, S or N-R₁ and R₁ is H, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, benzyl or β-phenylethyl;

B₁ and B₂ are each independently an optionally substituted hydrocarbon linkage containing from 1 to 10 carbon atoms;

10 D₁ is H or a primary amino, secondary amino, tertiary amino, quaternary ammonium, imidazole, guanidino or amidino group; and

D₂ is a secondary amino, tertiary amino, quaternary ammonium, imidazole, guanidino or amidino group; or

B₂-D₂ is -CHCOOH-(CH₂)₃₋₄-NH₂; and

15 p is 0 or 1.

2. A conjugate according to claim 1, wherein A₁ and A₂ are each independently N-R₁ wherein R₁ is as defined in claim 1.

3. A conjugate according to claim 2, wherein A₁ and A₂ are each NH.

4. A conjugate according to any preceding claim, wherein B₁ and B₂ are each independently -CHCOOH-(CH₂)₁₋₄- or a divalent ethyl, propyl, 2-hydroxypropyl, butyl, 20 pentyl, hexyl, phenyl, naphthyl or cyclohexyl group.

5. A conjugate according to claim 4, wherein B₁ and B₂ are each independently -CHCOOH-(CH₂)₃₋₄- or a divalent butyl, pentyl or phenyl group.

6. A conjugate according to any preceding claim, wherein D_1 is H, amino, imidazolyl, guanidino, aminidino, trimethylammonium, triethylammonium, dimethylamino, diethylamino, methylamino or ethylamino.

7. A conjugate according to any preceding claim, wherein D_2 is imidazolyl, guanidino, aminidino, trimethylammonium, triethylammonium, dimethylamino, diethylamino, methylamino or ethylamino.

8. A conjugate according to any preceding claim, wherein p is 1.

9. A conjugate according to any preceding claim, wherein each X is N.

10. A conjugate according to any preceding claim, wherein Z is

10



wherein T is O, S or NR_2 and R_2 is H or C_{1-6} alkyl;

V is O, S, $-COO-$, $CONH$, $NHCO$, $-PO_3H-$, NH -arylene- $SO_2-CH_2-CH_2-$ or $N-R_3$

15 and R_3 is H or C_{1-6} alkyl;

L is an optionally substituted hydrocarbon linkage containing from 2 to 20 carbon atoms; and

m is 0 or 1.

11. A conjugate according to claim 10, wherein R_2 and R_3 are each H.

20 12. A conjugate according to claim 10 or claim 11, wherein T is O or NH.

13. A conjugate according to claim 12, wherein T is NH.

14. A conjugate according to any of claims 9 to 13, wherein m is 1 and L is a divalent butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl or dodecyl group.

15. A conjugate according to any of claims 10 to 14, wherein m is 1 and V is O, $-CONH-$, $-NHCO-$ or $N-R_3$.

16. A conjugate according to claim 15, wherein V is O or NH.

17. A conjugate according to claim 16, wherein V is NH.

18. A conjugate according to claim 16 or claim 17, wherein $Z-M$ (M being the matrix) is $-NH-(CH_2)_{4-10}-NH-M$.

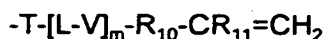
30 19. A conjugate according to claim 18, selected from any of formulae XXX to XXXX.

20. A conjugate according to any preceding claim, wherein the matrix is optionally tresyl-activated, sulphonyl chloride-activated, tosyl-activated, vinyl sulphone-activated or epoxy-activated.

21. An affinity ligand of formula (1) as defined in any of claims 1 to 9, wherein Z is a functional group capable of reaction with a solid matrix.

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22. A ligand according to claim 21, wherein the matrix is as defined in claim 20.
23. A ligand according to claim 22, wherein Z is F, Cl, Br or I.
24. A ligand according to claim 22, wherein Z is -NH-(CH₂)₂₋₂₀-NH₂.
25. A ligand according to claim 22, wherein Z is -NH-(CH₂)₂₋₂₀-(CO)₀₋₁-OH.
- 5 26. A ligand according to claim 22, wherein Z is



wherein T, L, V and m are as defined in any of claims 10 to 17;

- 10 R₁₀ is CO, CH₂, NH-CH₂- or -S-CH₂-; and
R₁₁ is H or C₁₋₆ alkyl.
27. A ligand according to claim 23, wherein Z is Cl, and each X is N.
28. A ligand according to claim 24, wherein each X is N.
29. A ligand according to claim 22, selected from any of formulae XVI to XXVI.
- 15 30. The use of an affinity ligand or conjugate according to any preceding claim, for the separation, isolation, purification, characterisation, identification or quantification of an endotoxin.
31. Use according to claim 30, for the removal of an endotoxin from water or an aqueous solution, body fluid, blood, plasma, solution of pharmaceutical products,
- 20 protein or other compound of biological origin.
32. Use according to claim 31, which comprises using the conjugate for the extracorporeal removal of endotoxin from whole blood or plasma, prior to re-infusion into the donor or another recipient.
33. Use according to any of claim 30 to 32, wherein the endotoxin originates from
- 25 a Gram-negative bacterium.
34. Use according to claims 30 to 35, wherein an endotoxin-containing solution or liquid is applied to the conjugate at a pH of 1.0 to 13.0.

INTERNATIONAL SEARCH REPORT

International Application No

T/GB 00/01759

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 B01J20/32 C02F1/28 C07K1/22 C07D251/50 C07D251/54
C07D403/12 C07D251/70 A61M1/36 G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 B01J C02F C07K G01N B01D C07D A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 10887 A (NOVO NORDISK) 27 March 1997 (1997-03-27) page 5, line 21 -page 6, line 31; claims 1,2,24,28,30,32,34 ---	1-4, 6-18, 20-28
X	BURTON N P ET AL: "DESIGN OF NOVEL AFFINITY ADSORBENTS FOR THE PURIFICATION OF TRYPSIN-LIKE PROTEASES" JOURNAL OF MOLECULAR RECOGNITION,GB,HEYDEN & SON LTD., LONDON, vol. 5, 1992, pages 55-68, XP000654088 ISSN: 0952-3499 page 58, paragraph 3 - paragraph 4 page 60; table 1 page 66; table 5 page 65; figure 4 --- -/-	1-3, 6-18, 20-24, 27,28

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

11 September 2000

Date of mailing of the international search report

18/09/2000

Name and mailing address of the ISA

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Authorized officer

Hilgenga, K

INTERNATIONAL SEARCH REPORT

International Application No

T/GB 00/01759

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	✓ WO 96 41185 A (PERSEPTIVE BIOSYSTEMS) 19 December 1996 (1996-12-19) claims 1,14,34,36 ---	1,6,7, 30-33
A	✓ GB 2 092 470 A (TANABE SEIYAKU) 18 August 1982 (1982-08-18) page 2, line 27 - line 32 page 13, line 15 - line 30 page 1, line 48 page 1, line 13 - line 19 ---	1-4, 7-18, 20-22, 24,25, 30,31,33
A	✓ EP 0 350 004 A (TANABE SEIYAKU) 10 January 1990 (1990-01-10) page 3, line 26 - line 56 page 4, line 43 - line 47; claim 1 ---	1,30,31, 33,34
A	US 4 229 537 A (L.T. HODGINS) 21 October 1980 (1980-10-21) column 5, line 1 - line 10 ---	
A	US 4 491 660 A (R.L. GENDRICH) 1 January 1985 (1985-01-01) claim 1 ---	
A	✓ EP 0 431 593 A (DAICEL CHEMICAL INDUSTRIES) 12 June 1991 (1991-06-12) -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

T/GB 00/01759

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9710887	A	27-03-1997	AU 702901 B	11-03-1999
			AU 6924296 A	09-04-1997
			CA 2232626 A	27-03-1997
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			DE 69010124 T	13-10-1994
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			DE 69015334 T	17-08-1995
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			JP 3238004 A	23-10-1991
			KR 9301609 B	06-03-1993
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			US 5136032 A	04-08-1992

REC'D 29 AUG 2001

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference REP06137WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/01759	International filing date (day/month/year) 09/05/2000	Priority date (day/month/year) 10/05/1999
International Patent Classification (IPC) or national classification and IPC B01J20/32		
Applicant PROMETIC BIOSCIENCES LTD. et al.		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 5 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 3 sheets.

- This report contains indications relating to the following items:
 - ☒ Basis of the report
 - ☐ Priority
 - ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - ☐ Lack of unity of invention
 - ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - ☐ Certain documents cited
 - ☐ Certain defects in the international application
 - ☒ Certain observations on the international application

Date of submission of the demand 04/12/2000	Date of completion of this report 27.08.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Pielka, I Telephone No. +49 89 2399 8357 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01759

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):
Description, pages:

1-36 as originally filed

Claims, No.:

1-35 as received on 22/05/2001 with letter of 21/05/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/01759

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
see separate sheet

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	31-35
	No:	Claims	1-30
Inventive step (IS)	Yes:	Claims	31-35
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-35
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re l t m V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Claim 1 relates to an affinity ligand-matrix conjugate comprising a matrix and a ligand having the general formula (I).

In order to establish novelty over D2 (BURTON N P ET AL: 'DESIGN OF NOVEL AFFINITY ADSORBENTS FOR THE PURIFICATION OF TRYPSIN-LIKE PROTEASES' JOURNAL OF MOLECULAR RECOGNITION, GB, HEYDEN & SON LTD., LONDON, vol. 5, 1992, pages 55-68, XP000654088) a disclaimer has been added. There is no basis in the application for this disclaimer so that the disclaimer has to be viewed as being added subject-matter. Disclaimers can only be accepted for establishing novelty over documents which are accidentally novelty-destroying, being in a remote technical field. However, D2 is not in a remote technical field, but is concerned with purification of biological products.

Thus the disclaimer has to be ignored and the claimed subject-matter of claim 1 lacks novelty over that of D2 as D2 discloses ligands which correspond to formula (I) when X is N, A₂ is NH, B₂ is phenyl, D₂ is amidino, A₁ is NR₁ and R₁ is methyl, β-phenylethyl or β-hydroxyethyl, D₁ is H and p is zero (see ligands 2, 3 and 4, especially Figure 4).

D1 or WO-A-97 10887 discloses an affinity ligand-matrix conjugate which corresponds to that of claim 1 when D₂ is an imidazole group. The group Q in D1 has to be considered as D₂, not R₄, R₅ and R₆. In D1 Q can be a benzimidazole ring and R₄, R₅ and R₆ are H.

Thus the subject-matter of claim 1 lacks novelty over both D1 and D2. Claim 1 does not meet the requirements of **Article 33(2) PCT**.

Claims 2 to 30, being dependent on claim 1, also do not meet the requirements of **Article 33(2) PCT**.

Claims 31 to 35 relate to the specific use of the known conjugates and ligands for the separation of endotoxins. This subject-matter is novel over that of D1 and D2 as no specific mention of endotoxins is disclosed in either document. It also appears that an inventive step can also be acknowledged for said subject-matter.

Re Item VIII

Certain observations on the international application

The subject-matter of the claims lacks clarity for the following reasons:

Claim 1:

In Formula (I) there is a group Z which is not defined.

Claims 20 and 30:

In these claims there are references to Formulae XXX to XXXX and XVI to XXVI.

These formulae are not defined in any way so that the subject-matter of these claims is not clear.

Claims 31 to 35:

Claims 32 to 35 depend on claim 31, but the use in claim 32 is for the removal of endotoxin which does not have an antecedent in claim 31.

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference REP06137W0	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 00/01759	International filing date (day/month/year) 09/05/2000	(Earliest) Priority Date (day/month/year) 10/05/1999
Applicant PROMETIC BIOSCIENCES LTD. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/01759

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 B01J20/32 C02F1/28 C07K1/22 C07D251/50 C07D251/54
C07D403/12 C07D251/70 A61M1/36 G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 B01J C02F C07K G01N B01D C07D A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 10887 A (NOVO NORDISK) 27 March 1997 (1997-03-27) page 5, line 21 -page 6, line 31; claims 1,2,24,28,30,32,34	1-4, 6-18, 20-28
X	BURTON N P ET AL: "DESIGN OF NOVEL AFFINITY ADSORBENTS FOR THE PURIFICATION OF TRYPSIN-LIKE PROTEASES" JOURNAL OF MOLECULAR RECOGNITION, GB, HEYDEN & SON LTD., LONDON, vol. 5, 1992, pages 55-68, XP000654088 ISSN: 0952-3499 page 58, paragraph 3 - paragraph 4 page 60; table 1 page 66; table 5 page 65; figure 4	1-3, 6-18, 20-24, 27,28

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

11 September 2000

Date of mailing of the international search report

18/09/2000

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Hilgenga, K

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/01759

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 41185 A (PERSEPTIVE BIOSYSTEMS) 19 December 1996 (1996-12-19) claims 1,14,34,36	1,6,7, 30-33
A	GB 2 092 470 A (TANABE SEIYAKU) 18 August 1982 (1982-08-18) page 2, line 27 - line 32 page 13, line 15 - line 30 page 1, line 48 page 1, line 13 - line 19	1-4, 7-18, 20-22, 24,25, 30,31,33
A	EP 0 350 004 A (TANABE SEIYAKU) 10 January 1990 (1990-01-10) page 3, line 26 - line 56 page 4, line 43 - line 47; claim 1	1,30,31, 33,34
A	US 4 229 537 A (L.T. HODGINS) 21 October 1980 (1980-10-21) column 5, line 1 - line 10	
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